Cost-effectiveness of Ivacaftor (Kalydeco™) for the treatment of cystic fibrosis in patients age 6 years and older who have the *G551D* mutation

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1. A rapid review submission on the drug ivacaftor (Kalydeco) was submitted by Vertex Pharmaceuticals UK Ltd to the National Centre for Pharmacoeconomics (NCPE) on the 13th August 2012. The rapid review was completed on the 22nd August 2012 and a full pharmacoeconomic assessment was advised. Following submission of the economic dossier the NCPE review group met with the manufacturer on the 28th November 2012 to discuss the submission and to request additional information. The additional data was received on the 11th December 2012.

2. Cystic fibrosis (CF) is a genetic condition caused by mutations in the CF transmembrane conductance regulator (CFTR) protein, an epithelial ion channel that contributes to the regulation of absorption and secretion of salt and water in tissues including the lung, sweat glands, pancreas and gastrointestinal tract. Ivacaftor is the first in a new class of drugs known as CFTR potentiators designed to increase the time that activated CFTR channels at the cell surface remain open.

3. Four studies were presented as evidence of the benefit of ivacaftor in CF. Two pivotal trials STRIVE and ENVISION, one open label extension study, PERSIST, for patients in STRIVE and ENVISION and a final study in a slightly different patient group, DISCOVER, in patients who are homozygous for the F508del mutation in the CFTR gene. The percent predicted forced expiratory volume in 1 second (FEV_1) was the primary outcome measure for the two phase III clinical trials.

4. The economic dossier was a cost utility analysis comparing ivacaftor plus standard of care (SOC) to SOC in CF patients aged 6 years and over with the G551D mutation. A patient-level simulation was constructed to estimate clinical outcomes and costs in this population of patients. The economic model used patient level data from the clinical trials (STRIVE and ENVISION) and the review group was satisfied that this was representative of the Irish population. The perspective of the analysis was that of the Irish healthcare payer – the Health Service Executive (HSE) and outcomes were estimated over a lifetime horizon.

5. There were three scenarios presented. The basecase analysis assumed the percent predicted FEV_1 of ivacaftor treated patients remained stable over time whereas it declined for patients on placebo. The review group considered this to be an overestimation of the benefit of ivacaftor. In scenario two the FEV_1 slope for the ivacaftor group over time was modelled at 50% of the standard of care and in scenario three the FEV_1 slope over time was set identical to the standard of care and the only benefit of ivacaftor was the immediate absolute increase in FEV_1 of approximately 10%. The main driver of the estimated effect of ivacaftor on survival was the difference in percent predicted FEV_1 progression between the treatment groups.

6. The review group noted the absence of long term efficacy data particularly in relation to the benefit of ivacaftor in maintaining percent predicted FEV_1 and reducing pulmonary exacerbations and the resultant impact on survival rates. The economic model was underpinned by the assumption that ivacaftor extended the life of a cystic fibrosis patient (i.e. halves the hazard of dying). The analysis for this extrapolation is based on a number of prediction models that have been published. The disease progression model predicts that the median survival for a patient treated with ivacaftor will be 29.2 years longer as a consequence of taking the drug.

7. The utility values measured as per FEV_1 category were normal (≥90%) 0.97, mild (70-89%) 0.95, moderate (40-69%) 0.93 and severe (<40%) 0.91. The review group noted the small changes between these stages of pulmonary function severity. In relation to costs it was difficult to assess the disaggregated costs for the model as they are not presented in this way.

8. The basecase incremental costs were estimated at €2,533,637 and the incremental QALYs were 5.64 giving an ICER of €449,035/QALY. In terms of life years gained (LYG) the ICER was estimated at €443,825/LYG. The review group considered the basecase an optimistic scenario as there is limited long term outcome data (96 weeks for adults and 72 weeks for children). The incremental costs associated with a conservative scenario were €2,456,033 and the incremental QALYs were 2.9 giving an estimated ICER of €855,437/QALY. This scenario assumes that the slope of the percent predicted FEV_1 versus age declines at the same rate as SOC and the only benefit of ivacaftor is assumed to be the immediate response in predicted FEV_1 % of

approximately 10%. Based on the available data this assumption would allow for most uncertainty associated with the clinical trial data.

9. The review group felt that uncertainty was not adequately accounted for with the provision of a limited one way sensitivity analysis and the absence of a probabilistic sensitivity analysis (PSA). In place of a PSA the company have submitted a further sensitivity analysis where the clinical trial cohort has been used to create a new dataset using bootstrapping. Mean and median residual life year gains were presented. The replication produced different baseline demographics only and did not vary all the other inputs to the model. The review group do not accept that this method fully explores the uncertainty and would need to review a PSA where the intervals for each parameter varied are presented. Furthermore a cost-effectiveness acceptability curve (CEAC) has not been presented**.**

10. Ivacaftor is a new treatment for cystic fibrosis patients with the G551D genotype which is present in approximately 11.6% of the Irish CF patient population, according to the submitted dossier. At an annual cost of €234,804 per patient we have estimated the budget impact for 113-120 patients, to allow for patients not genotyped and changes since 2010. Based on these figures and assuming that all eligible patients will be commenced on treatment the gross annual budget impact ranges from €26,532,852 to €28,176,480. The wholesaler markup on this budget impact ranges from €2,122,628 to €2,254,118 and the patient care fees will be in the region of €6,838 to €7,262. The company have presented higher estimates of patient numbers; in 2013 an estimated 121 patients increasing to 125 patients in 2017. If cost offsets are included the company estimate that the annual net budget impact in 2013 will be €28,172,303 increasing to €28,883,659 in 2017.

12. The ICERs for ivacaftor plus SOC versus SOC alone ranged from €449,035/QALY to €855,437/QALY. These ICERs are well outside the threshold of €45,000/QALY. Whilst ivacaftor may represent an innovation for the treatment of patients with cystic fibrosis there are significant uncertainties, including the absence of long term health outcome data.

13. In view of the very high drug acquisition cost, the significant budget impact, the absence of long term clinical data and the fact that the company has failed to demonstrate the cost-effectiveness of ivacaftor we cannot recommend reimbursement of ivacaftor at the submitted price of €234,804 per patient per annum. A mechanism such as a performance based risk sharing scheme and/or a significant reduction in price could facilitate access to ivacaftor treatment for cystic fibrosis patients with the G551D CFTR mutation.